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Kongeriget Danmark

Patent application No.: PA 2003 00885

Date of filing: 13 June 2003

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Title: Treatment of symptoms associated with bacterial vaginosis
IPC: -

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Susanne Morsing



PATENT- OG VAREMÆRKESTYRELSEN

13 JUNI 2003

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Treatment of symptoms associated with bacterial vaginosis

All patent and non-patent references cited in the present application are hereby incorporated by reference in their entirety.

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Field of Invention

10 The present Invention relates to a high saccharide concentration medicament and the uses hereof for the treatment, amelioration and/or prophylaxis of symptoms associated with bacterial vaginosis.

Background of Invention

15 Bacterial Vaginosis (BV) is a clinical syndrome characterised by malodorous discharge. Bacterial Vaginosis is the most common type of vaginal infection in women of reproductive age, accounting for 45 % of all vulvovaginal infections. Moreover, it has been related to a variety of upper genital tract infections and obstetrical complications. These include pelvic inflammatory disease (PID), post-Caesarean endometritis, posthysterectomy pelvic infection, chorioamnionitis, premature rupture of membranes (PROM) and preterm labour and delivery. The prevention of these infections for a woman and her child is an important issue in women's health (1).

20 25 Fifteen percent of gynaecologic patients and 10 – 30 percent of pregnant women have BV, whilst up to 60 percent of women visiting a clinic for sexually transmitted diseases are estimated to suffer from BV (1).

30

Bacterial Vaginosis has been associated with non-white race, sexual activity and the intra-uterine device, but no precise studies are available. There are indications of sexual transmission of the disease, but other routes are also indicated.

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The normal vaginal flora is dominated by lactobacilli which account for 95 percent of the bacteria present in the vagina, with other facultative and anaerobic bacteria present in only small numbers. Bacterial Vaginosis represents a complex change in the vaginal ecosystem characterised by a reduction in the prevalence and concentration of lactobacilli and an increase in the prevalence and concentration of *Gardnerella*

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- vaginalis*, anaerobic gram-negative rods, and *Mycoplasma hominis*. In BV, a flora consisting primarily of benign lactobacilli is replaced by a flora consisting of high concentrations of potentially virulent bacteria. Lactobacilli maintain the acid pH in the vagina by producing lactic acid which maintains a low pH of normally less than 4.5.
- 5 Low pH directly inhibits the growth of anaerobic organisms. Hydrogen peroxide-producing lactobacilli also appear to play a role in limiting *Gardnerella* and the anaerobic flora of the vagina (1). Moreover the especially virulent *Prevotella* and *Porphyromonas* species are present in particular high numbers in patients with BV (1).
- 10 When affected women are symptomatic, they complain predominantly of vaginal odour. The odour is described as fishy. Patients often refer to embarrassing vaginal odour especially after intercourse. About 90 percent of patients also notice a mild to moderate discharge. Pain symptoms are rare because the infection is not linked to inflammation of the tissue. Patients with BV may not display the symptoms that would normally alert their physicians to the infection. In fact, nearly half of the patients with BV do not complain of excess or malodorous vaginal discharge.
- 15

The diagnosis requires three of the following signs to be present:

- 20 1. A homogenous, white or grey, noninflammatory discharge that adheres to the vaginal wall.
2. The presence of clue cells (> 20 % of the epithelial cells in 400 x magnification) on microscopic examination of fresh smears.
3. The pH of vaginal secretions greater than or equals 4.7.
- 25 4. A fishy odour of vaginal discharge before or after adding of 10 % KOH.

Culture of *Gardnerella vaginalis* is not recommended as a diagnostic tool, as it is not specific.

- 30 A study showed that patients with BV had a 5.1-fold higher risk of post-partum endometritis following Caesarean section than did patients with a lactobacilli-dominant flora.

- 35 Patients with BV have a four times higher rate of vaginal-cuff cellulitis following abdominal hysterectomy than patients with a lactobacillus-dominant flora (1).

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- 5 The rate of post-abortion pelvic inflammatory disease was three times less in patients treated with a BV-effective antibiotic related to placebo-treated patients. Prematurity occurs 1.9 times more commonly, and premature rupture of membranes occurs 3.5 times more commonly in women with BV than in those without BV. BV bacteria are frequently isolated from amniotic fluid and could play a major role in premature delivery (1).
- 10 The established medicine offers the treatment of either of two antibiotics, clindamycin or metronidazole, either topically or by the oral route.
- 15 Metronidazole as a 7-day treatment has an 80 – 90 % cure rate after 1 month. Side effects are nausea, abdominal cramps and a metallic taste. The patient must refrain from alcohol intake, as it may produce antabuse effects. It is not recommended in the first trimester of pregnancy.
- 20 Clindamycin as a 7-day treatment has equal effects as metronidazole, and its side effects are less, though diarrhoea is possible. Concerns about *Clostridium difficile* colitis have prevented the widespread use.
- 25 Topical application through vaginal preparations has minimised side effects; however, this approach is more expensive.
- 30 The cure rate is high but a significant proportion of women suffer relapses and recurrences. There is some evidence that residual biochemical and microbiological abnormalities persist in these women (2).
- 35 Different alternative measures have been advised (live yoghurt bacteria, *Lactobacillus acidophilus* preparations, acetic acid flushes (several hits on the Internet). Studies of live yoghurt or *Lactobacillus acidophilus* have not demonstrated benefits (3).
- In US patent 6,440,949 a method for increasing the acidity in vagina is suggested. The method suggests to administer an amount of 2.5 % to 17 % (w/v) of one or more saccharides in an acidic medicament. The patent tests different concentrations

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of saccharides, but none of the concentrations shows a significant decrease in pH, and furthermore, none of the concentrations shows elimination of the odour causing bacteria, the Gram negative bacteria (G-b). In US 6,440,949 there is shown no relation between the concentration of the saccharide and the results obtained.

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Summary of Invention

The present invention relates to the treatment of one or more of the symptoms associated with bacterial vaginosis, in particular treatment or amelioration of the odour normally associated with bacterial vaginosis.

Accordingly, in one aspect the invention relates to the use of saccharide, said saccharide being fermented by lactic acid bacteria, for the preparation of a medicament for the treatment, amelioration and/or prophylaxis of one or more symptoms caused by bacterial vaginosis, wherein the medicament comprises at least 20 percent by weight of saccharide.

Furthermore, the high concentration of acid formed depresses the malign bacteria and prolongs the symptom-free period after treatment. If needed, the treatment can be prolonged without limitations as no adverse side effects occur.

In another aspect the invention relates to a method for the treatment, amelioration and/or prophylaxis of one or more symptoms associated with bacterial vaginosis in an individual, comprising administering an effective amount of a medicament comprising a saccharide to said individual, said saccharide being fermented by lactic acid bacteria, wherein the medicament comprises at least 20 percent by weight of said saccharide.

In yet another aspect the invention relates to a pharmaceutical composition for vaginal application, comprising a saccharide, wherein the saccharide constitutes at least 20 percent by weight of the pharmaceutical composition.

In a further aspect the present Invention relates to a kit-of-parts comprising the pharmaceutical composition as defined above and an anti-fungal agent and/or an antibacterial agent for simultaneous, sequential or separate use.

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In another aspect the invention relates to a kit-of-parts comprising the pharmaceutical composition as defined above and at least one pH measurement means, for measuring vaginal pH.

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Detailed description of the Invention

As described above, the present invention relates in one aspect to the use of saccharide, said saccharide being fermented by lactic acid bacteria, for the preparation 10 of a medicament for the treatment and/or prophylaxis of one or more symptoms caused by bacterial vaginosis, wherein the medicament comprises at least 20 percent by weight of saccharide.

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The symptoms associated with bacterial vaginosis may be:

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- A homogenous, white or grey, noninflammatory discharge that adheres to the vaginal wall
- A fishy odour from vagina
- Pruritus of vulva
- Pain

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By the term "symptoms associated with bacterial vaginosis" is meant that the medicament may be used for treating the symptoms, independent of whether the diagnosis of bacterial vaginosis has been established according to the criteria set forth above.

30

The present invention may be used for treating, ameliorating and/or preventing any one of the above symptoms, and in particular the symptom treated, ameliorated and/or prevented with the present invention is the fishy odour.

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The present Inventor has found that a high concentration of saccharides alleviates the symptoms associated with bacterial vaginosis and prolongs the period without symptoms after treatment. The medicament comprises at least 20 percent by weight of saccharide; it is, however, preferred that the saccharide medicament comprises even more saccharide. In a preferred embodiment the medicament is a saccharide

- 5 suspension or pure saccharide, such as a saturated saccharide suspension, such as dry powder in tablets or capsules. Accordingly, the medicament preferably comprises at least 25 percent by weight of the saccharide, such as at least 40 percent by weight of saccharide, such as at least 50 percent by weight of saccharide, such as at least 75 percent by weight of saccharide, such as at least 90 percent by weight of saccharide, such as at least 95 percent by weight of saccharide, such as at least 98 percent by weight of saccharide, such as 100 percent by weight of saccharide. The term "percent by weight" is used in its normal meaning, i.e. grammes (g) of saccharide in grammes of the medicament.
- 10 Furthermore, it is preferred that the medicament according to the invention also treats or prevents the bacterial vaginosis. This may be examined by measuring the vaginal pH. A vaginal pH is normally less than 4.5. Accordingly, a decrease in vaginal pH to below 4.7, more preferably below 4.5, is an indication that the bacterial vaginosis has been treated.
- 15
- 20 The saccharide according to the invention is any suitable saccharide, wherein the saccharide is fermented by lactic acid bacteria. Preferably the saccharide is not fermented by *Gardnerella vaginalis*.
- 25 Accordingly, in a preferred embodiment the saccharide is selected from a disaccharide and a monosaccharide, such as a saccharide selected from lactose and saccharose, preferably selected from lactose. When using lactose, it is preferred that the lactose is in its original disaccharide form, and not degraded.
- 30 The medicament may comprise one type of saccharide or a mixture of saccharides, wherein all saccharides are suitable according to the invention.
- 35 The medicament according to the invention is useful for treating, ameliorating, and/or preventing symptoms associated with bacterial vaginosis as defined above independent of the bacteria causing the vaginosis. In particular the medicament is used for treating, ameliorating and/or preventing symptoms caused by bacteria selected from *Gardnerella vaginalis*, Gram negative rods, and *Mycoplasma hominis*. More specifically the medicament is used for treating, ameliorating and/or preventing symptoms caused by bacteria selected from anaerobic Gram negative rods.

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- The medicament according to the invention is preferably applied directly into the vagina, and therefore, the medicament is preferably formulated for topical application. Accordingly, the medicament may have any suitable form for topical administration.
- 5 In one embodiment the medicament is in the form of a vaginal suppository gel. In another embodiment the medicament is in the form of a vaginal capsule. In yet another embodiment the medicament is in the form of a vaginal tablet. In a further embodiment the medicament is in the form of a suspension.
- 10 The medicament preferably comprises a pharmaceutical composition comprising a saccharide as described herein optionally mixed with suitable pharmaceutically acceptable additives and/or carriers.
- 15 Examples of pharmaceutically acceptable additives and carriers are polyethylene glycols, glycerol, agar agar, carrageenan, modified starches, and water. In particular it is preferred that the additives or carriers are not based on protein, since a protein source may counteract the beneficial effects of the medicament.
- 20 In one aspect the invention further relates to a pharmaceutical composition comprising the saccharide as described above in the concentrations described above and optionally further comprising pharmaceutically acceptable additives and/or carriers.
- 25 The pH of the pharmaceutical composition before application to the vagina is preferably in the range of from 5.5 to 8.0, such as from 6.5 to 7.5, more preferably about 7.0.
- 30 The conservation of the product is preferably secured by low water activity, optionally aseptic production and packaging, and if needed, sorbic acid or paraben preservatives.
- The medicament according to the invention has a long shelf life at ambient temperature.

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In a further aspect the invention relates to a method of treating, ameliorating and/or preventing symptoms associated with bacterial vaginosis, wherein the method comprises administering an effective amount of a medicament comprising a saccharide, wherein the saccharide is as defined above.

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The medicament may be administered one or more times per day, as necessary for a period of from 1 to 7 days, but if needed, the treatment can be prolonged without limitations.

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The medicament is preferably administered in dosages, wherein one dosage unit may be from 10 mg to 10 g of medicament. In a more preferred embodiment, the dosage unit is from 1-5 g of medicament.

15

The saccharides are the essential active component of the medicament according to the invention, and can fulfil the object of the invention. However, for some treatment regimens, it is preferred that the medicament further includes an effective amount of another medicament.

20

Accordingly, in one embodiment the medicament further includes an anti-fungal agent. Examples of anti-fungal agents are ketoconazole, terconazole, itraconazole, and fluconazole.

25

In another embodiment the medicament further includes an effective amount of an anti-bacterial agent. Examples of suitable anti-bacterial agents are metronidazole and clindamycin.

30

In another aspect the invention relates to a combination product or a kit-of-parts product comprising the pharmaceutical composition as defined above and an anti-fungal agent and/or an anti-bacterial agent for simultaneous, sequential or separate use. The anti-fungal and anti-bacterial agent is preferably as described above.

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In order to test the functionality of the medicament, the medicament of the invention may also be commercialised as a kit-of-parts comprising the pharmaceutical composition as defined above and at least one pH measurement means, for measuring vaginal pH.

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The pH measuring means is preferably a pH indicator strip, such as an indicator strip from Merck showing pH in the interval 4.0-7.0. The pH measuring means may be applied directly to the vaginal mucosa for measurement.

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Examples**Example 1**10 Vaginal suppository gel

Ingredients:

15	Lactose, spray-dried (alpha monohydrate)	40 %
	Macrogol (polyethylene glycols) 1000	5 %
	Macrogol (polyethylene glycols) 3000	5 %
	Parabens*	0.1 %
	Disodium hydrogen phosphate	0.1 %
20	Water	49.8 %
	pH 7.0	

*8:2 mixture of methyl- and propyl para hydroxy benzoate

25 The ingredients were mixed homogeneously, the resulting suspension was sterilised by means of heat and dispensed aseptically into sterile packaging.

1 dosage = 1 – 3 ml

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Example 2Vaginal suppository gel

5	Lactose, spray-dried (alpha monohydrate)	40 %
	Glycerol	15 %
	Agar agar	2 %
	Disodium hydrogen phosphate	0.1 %
	Water	42.9 %
10	pH 7.0	

The ingredients were heated to boiling point and mixed homogeneously. They were then sterilised by heat and dispensed aseptically into sterile packaging.

15 1 dosage = 1 – 3 ml

Example 3Vaginal suppository gel

20	Lactose, spray-dried (alpha monohydrate)	50 %
	Glycerol	15 %
	Carageenan (Iota or mixture)	0.8 %
	Disodium hydrogen phosphate	0.1 %
25	CaCl ₂	0.1 %
	Water	34 %
	pH 7.0	

30 The ingredients were heated to boiling point and mixed homogeneously. They were then sterilised by heat and dispensed aseptically into sterile packaging.

1 dosage = 1 – 3 ml

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Example 4Vaginal capsule

- 5 Lactose, spray-dried (alpha monohydrate)
 Encapsulated in capsules produced from modified starches

Capsules were prepared in a conventional manner.

- 10 Dosage: 0.5 – 3 grammes

Example 5Vaginal tablets

15	Lactose, Fast Flo	90 %
	Starch 1500 (modified starch)	10 %

- 20 The ingredients were mixed homogeneously, and the resulting mixture was pressed into tablets in a conventional manner. Raw materials of good microbiological quality and hygienic production facilities secure the required microbiological quality.

Dosage: 0.5 – 3 grammes

- 25 **Example 6**

Vaginal tablets

30	Lactose, spray-dried (alpha monohydrate)	95 %
	Polyethylene glycol	5 %

- 35 The ingredients were mixed homogeneously, and the resulting mixture was pressed into tablets in a conventional manner. Raw materials of good microbiological quality and hygienic production facilities secure the required microbiological quality.

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Dosage: 0.5 – 3 grammes**Example 7****5 Vaginal tablets**

Lactose, spray-dried (alpha monohydrate)	100 %
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10 The lactose was pressed into tablets in a conventional manner. Raw materials of good microbiological quality and hygienic production facilities secure the required microbiological quality.

Dosage: 0.5 – 3 grammes**15 Example 8****Suspension**

20 Lactose, spray-dried (alpha monohydrate)	50 %
Disodium hydrogen phosphate	0.1 %
Water	49.9 %
pH 7.0	

25 The ingredients were mixed homogeneously, and the resulting suspension was sterilised by means of heating.

1 dosage = 1 – 3 ml by use of an application device**30 Example 9****Treatment**

35 A female had suffered from discomfort and vaginal secretions of fishy smell recurring after two 7-day treatments with metronidazole. The vaginal pH was approximately 5.3, varying between 5.0 and 5.5.

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A lactose suspension (1-3 ml) as prepared in Example 8 was instilled into the vagina twice daily. After approximately 24 hours the pH lowered to 4.7 and the fishy odour disappeared. Continuous application once a day further lowered the pH down to approximately 4.4. The treatment was continued for 4 days.

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After 4 days symptoms such as the fishy odour recurred; however, the symptoms disappeared after one day of the treatment described above.

References

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1. SOGC Clinical Practice Guidelines No. 14 March 1997. Bacterial vaginosis.
2. Priestley, Cecilia JF, and GR Kinghorn. "Bacterial Vaginosis." *British Journal of Clinical Practice* 50, No. 6 (September 1996): 331-334.
3. Larsson, P.G. Treatment of bacterial vaginosis. *Int. J. STD AIDS* 1992; 3: 239-247.
4. *Gardnerella vaginalis* (2003) M. J. Pickett, James R. Greenwood, Sydney M. Harvey.

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Claims

1. Use of saccharide, said saccharide being fermented by lactic acid bacteria, for the preparation of a medicament for the treatment and/or prophylaxis of one or more symptoms caused by bacterial vaginosis, wherein the medicament comprises at least 20 percent by weight of saccharide.
- 5 2. The use according to claim 1, wherein one symptom is unpleasant vaginal odour, such as fishy-like odour.
- 10 3. The use according to any of the preceding claims, wherein a symptom is pruritus of vulva.
- 15 4. The use according to any of the preceding claims, wherein the saccharide is substantially not fermented by *Gardnerella vaginalis*.
5. The use according to any of the preceding claims, wherein the saccharide is selected from a disaccharide and a monosaccharide.
- 20 6. The use according to any of the preceding claims, wherein the saccharide is selected from lactose and saccharose, preferably selected from lactose.
- 7.. The use according to claim any of the preceding claims, wherein the medicament comprises at least 25 percent by weight of the saccharide.
- 25 8. The use according to claim any of the preceding claims, wherein the medicament comprises at least 40 percent by weight of saccharide.
9. The use according to claim any of the preceding claims, wherein the medicament comprises at least 50 percent by weight of saccharide.
- 30 10. The use according to claim any of the preceding claims, wherein the medicament comprises at least 75 percent by weight of saccharide.

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11. The use according to any of the preceding claims, wherein the bacterial vaginosis is caused by bacteria selected from *Gardnerella vaginalis*, Gram negative rods, and *Mycoplasma hominis*.
- 5 12. The use according to claim 9, wherein the bacterial vaginosis is caused by bacteria selected from anaerobic Gram negative rods.
13. The use according to any of the preceding claims, wherein the medicament is formulated for topical application.
- 10 14. The use according to any of the preceding claims, wherein the medicament is in the form of a vaginal suppository gel.
- 15 15. The use according to any of the claims 1-13, wherein the medicament is in the form of a vaginal capsule.
16. The use according to any of the claims 1-13, wherein the medicament is in the form of a vaginal tablet.
- 20 17. The use according to any of the claims 1-13, wherein the medicament is in the form of a suspension.
18. The use according to any of the preceding claims, wherein a dosage unit is from 10 mg to 10 g of medicament.
- 25 19. The use according to any of the preceding claims, wherein a dosage unit is from 1-5 g of medicament.
20. The use according to any of the preceding claims, wherein the medicament further includes an effective amount of an anti-fungal agent.
- 30 21. The use according to claim 20, wherein the anti-fungal agent is selected from ketoconazole, terconazole, itraconazole, and fluconazole.

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22. The use according to any of the preceding claims, wherein the medicament further includes an effective amount of an anti-bacterial agent.
- 5 23. The use according to claim 22, wherein the anti-bacterial agent is selected from metronidazole and clindamycin.
- 10 24. A method for the treatment, amelioration and/or prophylaxis of one or more symptoms associated with bacterial vaginosis, comprising administering an effective amount of a medicament comprising a saccharide, said saccharide being fermented by lactic acid bacteria, wherein the medicament comprises at least 20 percent by weight of said saccharide.
- 15 25. The method according to claim 24, said method comprising one or more of the features of claims 2-23.
- 20 26. A pharmaceutical composition for vaginal application, comprising a saccharide, wherein the saccharide constitutes at least 20 percent by weight of the pharmaceutical composition.
- 25 27. The pharmaceutical composition comprising one or more of the features of claims 2-23.
28. A kit-of-parts comprising the pharmaceutical composition as defined in claim 26 and an anti-fungal agent and/or an anti-bacterial agent for simultaneous, sequential or separate use.
29. A kit-of-parts comprising the pharmaceutical composition as defined in claim 26 and at least one pH measurement means, for measuring vaginal pH.

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